I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 6, 2008.

TOWNSEND and TOWNSEND and CREW LLP

By: Jo Dallara
Jo Ann Honcik Dallara

PATENT
Attorney Docket No. 026549-000100US
Client Ref. No. 30836

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Ronit Eisenberg
Raz Tamar

Application No.: 10/009,809

Filed: April 26, 2002

For: CELL PENETRATING ANTI-ALLERGIC PEPTIDES

Customer No. 20350

Confirmation No. 1519

Examiner: Crowder, Chun

Technology Center/Art Unit: 1644

APPELLANTS' BRIEF UNDER 37 CFR §41.37

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal mailed on February 8, 2008, for the above-referenced application, Appellants submit this Brief on Appeal with a request for a one-month extension of time, extending the due date until May 8, 2008. Should additional fees be required, the Commissioner is authorized to charge the undersigned's Deposit Acct. No. 20-1430.

TABLE OF CONTENTS

1. REAL PARTY IN INTEREST

The real parties in interest are the two co-assignees: Ramat at Tel-Aviv University LTD. and Allergene LTD of Israel.

2. RELATED APPEALS AND INTERFERENCES

There are no related appeals, interferences, or judicial proceedings at this time.

To fully comply with requirements recently set forth under *McKesson Information Solutions Inc. v. Bridge Medical Inc.*, 487 F.3d 897 (Fed. Cir.2007), appellants identify U.S. Pat. No. 7,112,568, which is based upon a later filed application and provisos out the subject matter of this invention. In addition, USSN 11/495,625 and USSN 11/214,588 have claims that overlap with the claims on appeal. In compliance with *McKesson*, appellants will address conflicting positions taken by the examiners by informing the examiners as appropriate.

3. STATUS OF CLAIMS

Claims 63-70 and 72-78 are pending. All the other claims, 1-62, 71, and 78-79 have been canceled. Claims 63-70 and 72-78 are rejected as obvious and are being appealed.

4. STATUS OF AMENDMENTS

The last amendment to the claims was the cancellation of claim 79 in the Amendment filed on October 22, 2007. The Examiner entered the Amendment in the final Office Action mailed on November 29, 2007. No further amendments have been entered.

5. SUMMARY OF CLAIMED SUBJECT MATTER

The pending claims are not separately appealed. There are two independent claims 63 and 74. This invention provides for an anti-allergy agent comprising a cell penetrating peptide [CPP] from Kaposi fibroblast growth factor [KFGF] fused to either of two specific inhibitors of mast cell activation, $G\alpha i_3$ or $G\alpha t$. Claim 74 recites both inhibitors. Claim 63 recites only $G\alpha i_3$ (Seq ID No. 1). Both claims 63 and 74 find support from: (i) original claim 30 (general use language); (ii) original claims 42 and 43 reciting the two inhibitors $G\alpha t$ or $G\alpha i_3$; and, (iii)

original claim 43 reciting the KFGF CPP. Support for the sequences of the two inhibitors is found on page 10 at lines 6-17. The KFGF CPP sequence finds support in the same table on page 10.

THE INVENTION:

This invention provides for an anti-allergy agent comprising a cell penetrating peptide [CPP] from Kaposi fibroblast growth factor fused to either of two specific inhibitors of mast cell activation, Gαt or $G\alpha i_3$. In a test of four different CPPs, the claimed CPP from Kaposi fibroblast growth factor [Seq ID No. 3] was surprisingly discovered to be the *only* CPP able to transport the two inhibitor domains [Seq ID Nos. 1 and 2] in a manner that **inhibited** mast cell activation.

Independent claim 74 is illustrative:

> 74. A method of inhibiting mast cell degranulation in a subject, the method comprising administering to the subject a pharmaceutically effective amount of a therapeutic agent, wherein said therapeutic agent comprises a complex molecule which comprises a peptide having a first segment having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:3) and a second segment having an amino acid sequence KENLKDCGLF (SEQ ID NO:2) or KNNLKECGLY (SEQ ID NO:1), said first segment being joined to said second segment through a linker, thereby inhibiting mast cell degranulation in the subject.

TECHNICAL OVERVIEW:

This invention provides for a novel anti-allergy agent. The agent works by inhibiting the release of histamines by mast cells (degranulation). Mast cell degranulation or secretion are at the heart of many serious allergies.

The claimed agents are a fusion of a cell penetrating peptide [CPP] with one of two different mast cell inhibitors. Cell penetrating peptides are a known class of peptides that can transport themselves across a cell membrane into the cytosol of a cell. The prior art teaches that CPPs can be fused to biologically active proteins and will facilitate their delivery into cells.

In the subject invention, the two mast cell inhibitors are in the prior art. They are designated $G\alpha i_3$ and $G\alpha t$ and are 9 and 10 amino acids long, respectively.

While cell penetrating peptides are known, the technology is not well understood. Both Examiners Nolan and Crowder acknowledged the field as unpredictable. Examiner Nolan wrote in the non-final Office Action of April 8, 2005, on page 4:

> Claims 44, 52-62 [are -sic] rejected under 35 U.S.C. §112, first paragraph, because the specification while being enabling for using the importation peptide AAVALLPAVLLALLAP, does not reasonably provide enablement for the use of any importation molecule to treat allergies. … Since applicant's working examples demonstrate unpredictability in the ability of the import peptide to successfully transfer the inhibitory degranulation peptide to mast cells in vitro it would require an undue amount of experimentation to practice the full scope of the claimed invention in vivo.

Examiner Crowder wrote on page 4 of the non-final Office Action mailed August 2, 2006:

> Claims 63-70, 72-74 and 77-80 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement … The state of the art recognizes that the effect of cell-penetrating peptides can be unpredictable due to limited knowledge of the mechanisms associated with mast cell exocytosis.

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. The Examiner rejects the pending claims as obvious over Holgate in view of Aridor and Lin. Holgate is relied upon as generally teaching that pharmacological agents can inhibit mast cell degranulation and these agents are useful for treating diseases such as asthma. Aridor teaches Seq. No. 1 (KNNLKECGLY) and Seq. No. 2 (KENLKDCGLF). Lin teaches, Seq. ID No. 3, the Kaposi Fibroblast Growth Factor CPP (AAVALLPAVLLALLAP).

Dependent claims 64 and 65 reciting specific modifications are rejected as obvious over Holgate in view of Aridor and Lin in view of Avruch and Jackson. Avruch and Jackson recite modifications analogous to the those of dependent claims 64 and 65.

The Examiner presents the *prima facie* case of obviousness by arguing that she has identified the salient elements of the claims, a motivation to combine the elements, and a

reasonable expectation that once combined, the recited elements would function to inhibit histamine release by mast cells. Appellants request that claims 64 and 65 be considered jointly with the independent claims.

B. There is a provisional double patenting rejection. The Examiner provisionally rejected the pending claims over co-pending applications 10/465,826 (now U.S. Pat. No. 7,112,568), and 11/214,588. This rejection is not presented for appeal and will be addressed in an appropriate manner presuming that the single rejection under §103 is reversed.

7. ARGUMENT

Appellants submit that the *prima facie* case of obviousness is not properly set forth. The Examiner's presumption that the art is sufficiently predictable to provide one of skill with a reasonable expectation of success is wrong. In contrast to the Examiner's unsupported position, experimental evidence clearly indicates that most fusions of CPP with mast cell inhibitors do not inhibit mast cell degranulation. Alternatively, appellants seek to traverse the *prima facie* case of obviousness by surprising results. The fact that only one of the four CPPs tested successfully delivered a biologically active inhibitor was a surprise.

More specifically, appellants urge that the ability of CPPs to successfully deliver a *specific* biological agent needs to be empirically determined. The appellants' own work and the published work of others clearly demonstrated that only the claimed CPP [KFGF] fusion peptides inhibit mast cell secretion. The other three CPPs tested did not work to inhibit mast cell degranulation.

The following table provides a summary of the experimental results. The first six fusions were reported in the subject application, and the last fusion was reported in the academic literature:

CHIMERIC PEPTIDE			RESULTS
Hu Int	$G\alpha i_3$	SEQ ID NO: 6	No inhibition of histamine secretion
KFGF	$G\alpha i_3$	SEQ ID NO: 7	**Inhibited histamine secretion**
Dros	$G\alpha i_3$	SEQ ID NO: 10	Induced histamine secretion
Hu Int	$G\alpha t$	SEQ ID NO: 11	No inhibition of histamine secretion
KFGF SEQ ID NO: 3	$G\alpha t$	SEQ ID NO: 12	**Inhibited histamine secretion**
Dros	$G\alpha t$	SEQ ID NO: 13	Induced histamine secretion
TP-10	$G\alpha i_3$	Jones *et al.*	Induced histamine secretion

Two Rule 132 declarations were submitted to support this conclusion. The first declarant is Dr. Ehud Razin. He is a non-inventor, a professor of Biochemistry at Hebrew-University, and an expert in mast cells. The second declarant is Dr. Ronit Eisenberg. Dr. Eisenberg is a co-inventor and professor at Tel Aviv University.

By argument and two Rule 132 Declarations, appellants explained that the unpredictability of the two mast cell inhibitor peptides to inhibit mast cell secretion once fused to a CPP arises from a variety of unpredictable factors. It was explained that once CPP penetration has occurred, the biological effect of the mast cell inhibitor cargo peptide on the mast cell can be influenced by: (i) conformation changes associated with the fusion; (ii) degradation of the "foreign" peptide in the cell; (iii) sequestering of the fusion peptide in an endosome; or, (iv) ability of the CPP to trigger mast cell release.

The Examiner expressly ignored the experimental data and the two Rule 132 Declarations explaining in scientifically object terms why the biological effect of any specific CPP is unpredictable.

The Examiner argues that she is entitled to focus entirely on the teachings of Lin, disclosing the Kaposis' CPP (AAVALLPAVLLALLAP), and ignore the negative results from the other three CPPs. In effect, she renders the *prima facie* case of obviousness irrebuttable. She writes on page 4 of the Final Office Action mailed on November 29, 2007:

> In this case, the data (that shows other CCP [CPP-sic] peptides fail to inhibit histamine secretion is inadequate evidence that the claimed CCP of SEQ ID NO:3 is unpredictable. Even if the field of CPP technology is unpredictable, the instant SEQ ID No.:3 has been consistently shown to be predictable in delivery of biological cargo peptides and maintaining the functions of said peptides (see Lin et al. and the Sagi-Eisenberg declaration and Razin declaration filed on June 28, 2007).

A proper prima facie case of obviousness is by definition rebuttable. This Board stated in *Ex parte Ohsaka*:

> The flaw with this approach is that the examiner has, in practical effect, converted a rebuttable presumption into a conclusive or irrebuttal presumption of obviousness…
>
> when prima facie obviousness has been established and evidence is submitted in rebuttal, the decision-maker must start over...An earlier decision should not, as it was here, be considered as set in concrete...[T]he examiner must consider all the evidence anew. 2 USPQ 2d 1461, 1462 (PTOBPA&I 1987).

The Examiner's selective focus on the Lin disclosure of the Kaposi CPP arises from no objective, scientific rationale focusing those of skill on the Kaposi CPP. More specifically, the prior art does not favor or recommend the Lin CPP over the other CPPs. There is nothing in the declarants' statement to support the Examiner's position. The two declarants state in ¶5 that prior to the appellants' work, all the CPPs were considered to be essentially equivalents. Both Declarents wrote:

> Because the prior art literature would suggest to those of skill that CPPS are interchangeable, it is surprising that the choice of CPP would be critical for obtaining biological activity.

In other words, no reference says that the Lin CPP is better than the other CPPs. It was the appellants' experimental work that determined this—at least for the two mast cell inhibitors recited in the rejected claims.

This rejection reflects a serious misunderstanding of the law relating to traversing a *prima facie* case of obviousness. An examiner cannot ignore the rebuttal argument and selectively focus on references that support his/her position. *Akzo N.V. v USITC*, 1 USPQ 2d 1241(CAFC 1986). The Federal Circuit stated on page 1246:

> ...prior art references before the tribunal must be read as a whole and consideration must be given where the references diverge and teach away from the claimed invention.

Similarly, there is *Application of Lunsford*, 357 F.2d 385, 389-390; 148 USPQ 721, 724 (CCPA 1966). *Lunsford* tells us that if a reference is to be ignored, the Examiner must cite specific references proving that the ignored reference should be ignored. It is not sufficient to summarily disregard the reference. The CCPA stated:

> All of the facts must be considered and it is not realistic within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

Here, the Examiner has been provided with evidence of unpredictability based on experimental evidence but has not refuted that evidence in any objective manner. The sole argument supporting the obviousness rejection is the Examiner's belief that contrary experimental evidence need not be considered and that the rejection is properly based solely on the three references identified herein. This position of *ignoring* contrary evidence is clearly improper under the law concerning obviousness rejection. That law requires examiners consider all the facts and the rejection be reviewed anew. *Application of Kuderna*, 426 F.2d 385 at 389 (CCPA 1970).

The appellants' evidence presents a classic fact pattern for traversing a *prima facie* case of obviousness. Unlike the recent, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir. 2007), this is not a situation of someone selecting the *best* combination from a limited group of choices (salts) all of which were known to work to some degree. Here the other choices (CPPs) *do not* work. According to the literature, any CPP should have worked; but, three of the four CPPs did not work when fused with the two mast cell inhibitors being claimed.

The evidence presented by appellants can be viewed as both rebutting and traversing the *prima facie* case of obviousness. The Board may view the contrary data as evidence of the unpredictability of the relevant art leading to a conclusion that the *prima facie* case of obviousness is incomplete. Alternatively, the Board may view the totality of the results as sufficiently surprising in view of the number of non-working embodiments that the *prima facie* case of obviousness has been traversed. Both declarants state in their concluding paragraphs:

> For these reasons, I conclude without hesitation that the claimed combinations of AAVALLPAVLLALLAP with either $G\alpha i_3$ or $G\alpha t$ to yield a functional inhibitory effect on mast cell activation in light of failure with three other CCP's [sic-CPP's] of equal status was **unpredictable, surprising** and of great value. [emphasis added]

Either analysis leads to the same result. The obviousness rejection over Holgate, in view of Aridor and Lin, should be withdrawn.

Appellants respectfully submit that the rejection is not legally proper and request reconsideration and withdrawal of this basis for rejection under §103. The other rejections are dependent upon this §103 rejection. If the reviewing panel agrees with the appellants' position, the claims should be in condition for allowance.

8. CONCLUSION

For these reasons, it is respectfully submitted that the rejection should be reversed.

Respectfully submitted,

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9. CLAIMS APPENDIX

Claims 1-62 (cancelled).

63. (Previously presented) A method of inhibiting mast cell degranulation in a subject, the method comprising administering to the subject a pharmaceutically effective amount of a therapeutic agent, wherein said therapeutic agent comprises a complex molecule which comprises a first segment having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 3) linked via a linker to a second segment having an amino acid sequence KNNLKECGLY (SEQ ID NO:1), thereby inhibiting mast cell degranulation in the subject.

64. (Previously presented) The method of claim 63, wherein said complex molecule is a peptide having an amino acid sequence AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:7) and comprises a cyclization between lysine at position 17 and the C terminus of the peptide.

65. (Previously presented) The method of claim 63, wherein said complex molecule is a peptide having an amino acid sequence AAVALLPAVLLALLAPKNNLKECGLY (SEQ ID NO:7) and comprises a succinyl residue at the N terminus of the peptide.

66. (Previously presented) The method of claim 63, wherein the mast cell degranulation is associated with a condition selected from the group consisting of nasal allergy, an allergic reaction in an eye of the subject, an allergic reactions in the skin of the subject, acute urticaria, psoriasis, psychogenic or allergic asthma, interstitial cystitis, bowel diseases, migraines, and multiple sclerosis.

67. (Previously presented) The method of claim 63, wherein the step of administration of said therapeutic agent is performed by topical administration.

68. (Previously presented) The method of claim 67, wherein said topical administration is to the eye, the skin or to a mucous membrane of the subject.

69. (Previously presented) The method of claim 63, wherein administration of said therapeutic agent is performed by inhalation or by intranasal administration.

70. (Previously presented) The method of claim 63, wherein administration of said therapeutic agent is performed by oral or systemic parenteral administration.

71. (Canceled).

72. (Previously presented) The method of claim 63, wherein said linker is a covalent bond.

73. (Previously presented) The method of claim 72, wherein said covalent bond is a peptide bond.

74. (Previously presented) A method of inhibiting mast cell degranulation in a subject, the method comprising administering to the subject a pharmaceutically effective amount of a therapeutic agent, wherein said therapeutic agent comprises a complex molecule which comprises a peptide having a first segment having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO:3) and a second segment having an amino acid sequence KENLKDCGLF (SEQ ID NO:2) or KNNLKECGLY (SEQ ID NO:1), said first segment being joined to said second segment through a linker, thereby inhibiting mast cell degranulation in the subject.

75. (Previously presented) The method of claim 74, wherein said mast cell degranulation is IgE-dependent.

76. (Previously presented) The method of claim 74, wherein said mast cell degranulation is IgE-independent.

77. (Previously presented) The method of claim 63, wherein said mast cell degranulation is IgE-dependent.

78. (Previously presented) The method of claim 63, wherein said mast cell degranulation is IgE-independent.

79. (Canceled).

80. (Canceled).

10. EVIDENCE APPENDIX

Rule 132 Declaration by Ronit Sagi-Eisenberg filed June 28, 2007, and entered in the non-final office action dated September 5, 2007.

Rule 132 Declaration by Ehud Razin filed June 28, 2007, and entered in the non-final office action dated September 5, 2007.

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On _____

TOWNSEND and TOWNSEND and CREW LLP

By:_____

PATENT
Docket No.: 026549-000100US
Client Ref. No.: 30836

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1519
Ronit Eisenberg	Examiner: Crowder, Chun
Patent No.:	Art Unit: 1644
Issued:	RULE 132 DECLARATION
Application No.: 10/009,809	
Filed: April 26, 2002	
For: CELL PENETRATING ANTI-ALLERGIC PEPTIDES	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Ronit Sagi-Eisenberg, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. **The Exhibits (1 and _ attached hereto are incorporated herein by reference.**

2. I received a Ph.D. in Biochemistry from the University of Tel Aviv in 1980 .

A copy of my curriculum vitae is attached as Exhibit 1.

3. I am presently employed at Tel Aviv University and am primarily responsible for teaching and research.

4. I have read and am familiar with the contents of the application. I understand that the Examiner has a single rejection based on obviousness that is based on a combination of three references. The references are Holgate as a primary reference in view of Aridor and Lin. Holgate is cited as disclosing that agents that inhibit mast cell degranulation are recognized for treatment of diseases such as asthma. Aridor discloses KNNLKECGLY which is a mast cell activation inhibitor designated Gαi3 C-terminal peptide. Lin discloses the preferred cell penetrating peptide from Kaposi fibroblast growth factor [KFGF].

5. This invention is the surprising discovery that of four different cell penetrating peptides (CCP) only one CCP was able to successfully deliver two mast cell activation inhibitors in a biologically active manner. Because the prior art literature would suggest to those of skill that CCPs are interchangeable, it is surprising that the choice of CCP would be critical for obtaining biological activity. Accordingly, we have to conclude that the field of using cell penetrating peptides to deliver biologically active proteins is far less predictable than the Examiner believes it to be and that the applicants' results as embodied in the pending claims are both surprising and advantageous.

The following statements provide objective, scientific reasons for the above conclusion.

6. It is my understanding that the rejection of the pending claims is based on the proposition that Lin's teaching of the CCP, (AAVALLPAVLLALLAP) as a tool for delivery of biologically active cargo peptides renders the claimed combinations of AAVALLPAVLLALLAP in reading frame fusions with $G\alpha i_3$ or Gαt C-terminal peptides obvious and unpatentable. In brief, the Examiner believes that upon reading the three references, one of skill would be motivated by Holgate to combine the KFGF CCP of Lin with the mast cell activation inhibitor of Aridor, $G\alpha i_3$, with a reasonable expectation that the combination would inhibit mast cell activation.

It is also my understanding that evidence of unpredictability or surprising results can legally refute this conclusion and lead to the rejection being withdrawn.

It is my further opinion that both unpredictability and surprising results have been demonstrated by the applicants' work and by the literature already of record.

7. More specifically, we know that of the four CCPs tested only one CCP was able to deliver the two mast cell activation inhibitors, $G\alpha i_3$ or Gαt, as a biologically active inhibitors. The table below summarizes Applicants' results as described in the specification and in the Jones et al. publication.

CHIMERIC PEPTIDE			RESULTS
Hu Int	$G\alpha i_3$	SEQ ID NO: 6	No inhibition of histamine secretion
KFGF	$G\alpha i_3$	SEQ ID NO: 7	**Inhibited histamine secretion**
Dros	$G\alpha i_3$	SEQ ID NO: 10	Induced histamine

			secretion
Hu Int	Gαt	SEQ ID NO: 11	No inhibition of histamine secretion
KFGF SEQ ID NO: 3	Gαt	SEQ ID NO: 12	**Inhibited histamine secretion**
Dros	Gαt	SEQ ID NO: 13	Induced histamine secretion
TP-10	$G\alpha i_3$	Jones *et al.*	No inhibition of beta-hexoseaminidase secretion

8. From this data, it is clear that only Lin's CCP, KFGF is able to both deliver mast cell activation inhibitors and maintain their biological activity as inhibitors of mast cell activation . The Examiner says that this is predictable from the literature. I respectfully disagree.

Lin discloses that KFGF sequence transported two biologically active cargo peptides and generally states that KFGF can be used to transport other peptides. But similar reports exist for each of the other CCPs tested by applicants. The Hawiger review article discloses that the CCP designated integrin β_3 is just as able as KFGF to transport functional peptides into a cell (see page 189, 2nd column). Finally Derossi *et al.* describes the *Drosophila* CCP as successfully delivering biologically active compounds inside live cells (page 18188, 2nd col).

From page 7 of the Office Action, the Examiner appears to interpret this literature as leading one of skill to believe that there is a reasonable expectation that any

combination of CCP with any biologically active peptide will lead to the observation of biological activity in a cell.

I respectfully disagree. There are several scientific and objective reasons why fusing a CCP to a biologically active peptide might not result in observation of expected biological activity. These reasons include improper folding of the fusion peptide resulting in conformational changes that render the cargo peptide inactive; the degradation of the foreign peptide; sequestering of the peptide a endosomes or the ability of the CCP sequence to trigger a biological response, such as mast cell degranulation (e.g. positively charged CCP might function as basic secretagogues of mast cells).

Indeed, this appears to be the case for fusion of CCP with either $G\alpha i_3$ or $G\alpha t$. The data from applicants' laboratory and from the Jones *et al.* group demonstrate that not any CCP can maintain the biological activity of $G\alpha i_3$ or $G\alpha t$. Of four CCPs, only KFGF was the only CCP able to both internalize and maintain the inhibitory activity of both $G\alpha i_3$ and $G\alpha t$. Thus the combination provides a surprisingly advantageous result that was not predictable from the prior art.

I do note the Examiner's statement on page 7 that the table on page 9 with reference to the prior literature describing the various CCPs fail to demonstrate that Lin's CCP is unpredictable as a delivery tool. While this is true, there was no academic reason *a priori* to believe that any of the other CCPs would fail to deliver $G\alpha i_3$ and $G\alpha t$ while maintaining its expected biologically activity. But the evidence established by the record indicates that this is not true. There is obviously something special about the two mast cell activation inhibitors or with Lin's CCP that makes the claimed combination functional compared to the other three CCPs.

For these reasons, I conclude without hesitation that the claimed combinations of AAVALLPAVLLALLAP with either $G\alpha i_3$ or $G\alpha t$ to yield a functional inhibitory effect on mast cell activation in light of failure with three other CCPs of equal status was unpredictable, surprising and of great value.

This Declarant has nothing further to say.

Dated: May 6 2007

Dr. Ronit Sagi-Eisenberg

Ronit Sagi-Eisenberg

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NO. OF CHILDREN	status	children

A. EDUCATION

PERIOD OF STUDY (DATES)	
1970 - 1973	**Tel Aviv University, Tel Aviv, Israel** **Chemistry** (Subject) **B.Sc.** (Degree) **1974** (Date Awarded)
1974 - 1975	**Tel Aviv University, Tel Aviv, Israel** **Biochemistry** (Subject) **M.Sc. studies-upgraded to Ph.D.**
1975-1980	**Tel Aviv University, Tel Aviv, Israel** **Bioenergetics** (Subject) **Ph.D.** (Degree)
Title of Doctoral Dissertation	Kinetic and energetic aspects of the Q cycle model.
Names of Supervisors	Name **Menachem Gutman** Title **Professor Emeritus**

B. ACADEMIC AND PROFESSIONAL EXPERIENCE	
PERIOD (DATES)	
1975-1980	**Tel Aviv University, Tel Aviv, Israel** **Chemistry** (Subject) **Biochemistry** (Department) **Teaching Assistant** (Rank/Function)
1980-1984	**The Weizmann Institute of Science, Rehovot, Israel.** **Mast cell biology** (Subject) **Chemical Immunology** (Department) **Post Doctoral fellow at the laboratory of Prof. I. Pecht.** (Rank/Function)
08/82-11/82 **08/83-11/83**	**University College London, London, U.K** **Mast cell biology** (Subject) **Pharmacology** (Department) **Honorary Research Assistant at the laboratory of Prof. J. Foreman.** (Rank/Function)
1984-1985	**The Weizmann Institute of Science, Rehovot, Israel.** **Mast cell biology** (Subject) **Chemical Immunology** (Department) **Investigator** (Rank/Function)
1985-1989	**The Weizmann Institute of Science, Rehovot, Israel.** **Signaling mechanisms underlying mast cell exocytosis.** (Subject) **Chemical Immunology** (Department) **Senior Investigator** (Rank/Function)
1989-1991	**The Weizmann Institute of Science, Rehovot, Israel.** **Signaling mechanisms underlying mast cell exocytosis.** (Subject) **Chemical Immunology**

	(Department) **Associate Professor** (Rank/Function)
1991-1994	**National Institutes of Health, Bethesda, MD, USA** **Mast cell exocytosis.** (Subject) **Laboratory of Chemical Pharmacology** (Department) **Visiting scientist at the Laboratory of Dr. Michael Beaven** (Rank/Function)
1994-present	**Tel Aviv University, Tel Aviv, Israel** **The interplay between trafficking and signaling; clinical applications.** (Subject) **Cell and Developmental Biology** (Department) **Associate Professor** (Rank/Function)

C. MEMBERSHIP IN PROFESSIONAL SOCIETIES	
Year	Society
1985-1991	The Israel Biochemical Society
1994-present	The Israel Society for Cell Biology
1997	The American Society of General Physiologists.

D. ADMINISTRATIVE DUTIES	
1995-1999	Member of the Animal Care and Use Committee
1996-1999	Treasurer of the Israel Society for Cell Biology
1997-2001	Preclinical Advisor for the Sackler School of Medicine, New York State/American Program
1998-2001	Member of the Teaching Committee of the Sackler School of Medicine, New York State/American Program
1998-present	Member of the Research and Development Committee of the Sackler Faculty of Medicine.
1998-2006	Head of the Sackler Faculty of Medicine Committee for Laboratory Space
1998-2006	Member of the Search Committee of the Sackler Faculty of Medicine
1999-present	Head of Admission Committee, Graduate program, Occupational Therapy
2002-present	Member of the Teaching Committee of the School of Continuing Medical Education
2002-2006	Member of the Ph.D. students committee

2002-present	Member of the University Committee of Intellectual property.
2005-present	Head of the Dept. of Cell and Developmental Biology,
2006- present	Member of the Sackler Faculty of Medicine committee for Scholarships.
2006-present	Member of the Sackler Faculty of Medicine board.
2006-present	Head of the Dr. Miriam and Sheldon G. Adelson Gradu School of Medicine.

E. FIELDS OF INTEREST
Signal Transduction, Protein Traffic, Allergic and Inflammatory diseases, Cancer

SCIENTIFIC PUBLICATIONS

A. ORIGINAL ARTICLES

A.1 Articles Published

1. **Sagi-Eisenberg, R.** and Gutman, M.
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B. INVITED REVIEW ARTICLES IN JOURNALS

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"The dual role of protein kinase C in the stimulus-secretion coupling of basophils".
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2. Aridor, M. and **Sagi-Eisenberg, R.**
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C. CHAPTERS IN BOOKS

1. Pecht, I., **Sagi-Eisenberg, R.** and Mazurek, N.
"Modulation of Calcium Ions Fluxes as Signals for Mast Cells and Basophils Degranulation".
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4. **Sagi-Eisenberg, R.,** Traub, L.M., Gat-Yablonski, G. and Aridor, M.
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7. **Sagi-Eisenberg, R.**
"Protein kinase C and Diacylglycerol".
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"Activation of heterotrimeric GTP-binding proteins.
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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to:

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

On _____

TOWNSEND and TOWNSEND and CREW LLP

By: _____

PATENT
Docket No.: 026549-000100US
Client Ref. No.: 30836

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 1519
Ronit Eisenberg	Examiner: Crowder, Chun
Patent No.:	Art Unit: 1644
Issued:	RULE 132 DECLARATION
Application No.: 10/009,809	
Filed: April 26, 2002	
For: CELL PENETRATING ANTI-ALLERGIC PEPTIDES	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Dr. Ehud Razin, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true and statements made on information or belief are believed to be true. **The Exhibits (1 and _ attached hereto are incorporated herein by reference.**

2. I received a Ph.D. in Immunology/Cell Biology from the Weizmann Institute of Science in 1980.

A copy of my curriculum vitae is attached as Exhibit 1.

3. I am presently employed at the Hebrew University of Jerusalem and am primarily responsible for teaching and research.

4. I have read and am familiar with the contents of the application. I understand that the Examiner has a single rejection based on obviousness that is based on a combination of three references. The references are Holgate as a primary reference in view of Aridor and Lin. Holgate is cited as disclosing that agents that inhibit mast cell degranulation are recognized for treatment of diseases such as asthma. Aridor discloses KNNLKECGLY which is a mast cell activation inhibitor designated Gαi3 C-terminal peptide. Lin discloses the preferred cell penetrating peptide from Kaposi fibroblast growth factor [KFGF].

5. This invention is the surprising discovery that of four different cell penetrating peptides (CCP) only one CCP was able to successfully deliver two mast cell activation inhibitors in a biologically active manner. Because the prior art literature would suggest to those of skill that CCPs are interchangeable, it is surprising that the choice of CCP would be critical for obtaining biological activity. Accordingly, we have to conclude that the field of using cell penetrating peptides to deliver biologically active proteins is far less predictable than the Examiner believes it to be and that the applicants' results as embodied in the pending claims are both surprising and advantageous..

The following statements provide objective, scientific reasons for the above conclusion.

6. It is my understanding that the rejection of the pending claims is based on the proposition that Lin's teaching of the CCP, (AAVALLPAVLLALLAP) as a tool for delivery of biologically active cargo peptides renders the claimed combinations of AAVALLPAVLLALLAP in reading frame fusions with $G\alpha i_3$ or Gαt C-terminal peptides obvious and unpatentable. In brief, the Examiner believes that upon reading the three references, one of skill would be motivated by Holgate to combine the KFGF CCP of Lin with the mast cell activation inhibitor of Aridor, $G\alpha i_3$, with a reasonable expectation that the combination would inhibit mast cell activation.

It is also my understanding that evidence of unpredictability or surprising results can legally refute this conclusion and lead to the rejection being withdrawn.

It is my further opinion that both unpredictability and surprising results have been demonstrated by the applicants' work and by the literature already of record.

7. More specifically, we know that of the four CCPs tested only one CCP was able to deliver the two mast cell activation inhibitors, $G\alpha i_3$ or Gαt, as a biologically active inhibitors. The table below summarizes Applicants' results as described in the specification and in the Jones et al. publication.

CHIMERIC PEPTIDE			RESULTS
Hu Int	$G\alpha i_3$	SEQ ID NO: 6	No inhibition of histamine secretion
KFGF	$G\alpha i_3$	SEQ ID NO: 7	**Inhibited histamine secretion**
Dros	$G\alpha i_3$	SEQ ID NO: 10	Induced histamine

			secretion
Hu Int	Gαt	SEQ ID NO: 11	No inhibition of histamine secretion
KFGF SEQ ID NO: 3	Gαt	SEQ ID NO: 12	**Inhibited histamine secretion**
Dros	Gαt	SEQ ID NO: 13	Induced histamine secretion
TP-10	$G\alpha i_3$	Jones *et al.*	No inhibition of beta-hexoseaminidase secretion

8. From this data, it is clear that only Lin's CCP, KFGF is able to both deliver mast cell activation inhibitors and maintain their biological activity as inhibitors of mast cell activation . The Examiner says that this is predictable from the literature. I respectfully disagree.

Lin discloses that KFGF sequence transported two biologically active cargo peptides and generally states that KFGF can be used to transport other peptides. But similar reports exist for each of the other CCPs tested by applicants. The Hawiger review article discloses that the CCP designated integrin β_3 is just as able as KFGF to transport functional peptides into a cell (see page 189, 2nd column). Finally Derossi *et al.* describes the *Drosophila* CCP as successfully delivering biologically active compounds inside live cells (page 18188, 2nd col).

From page 7 of the Office Action, the Examiner appears to interpret this literature as leading one of skill to believe that there is a reasonable expectation that any

combination of CCP with any biologically active peptide will lead to the observation of biological activity in a cell.

I respectfully disagree. There are several scientific and objective reasons why fusing a CCP to a biologically active peptide might not result in observation of expected biological activity. These reasons include improper folding of the fusion peptide resulting in conformational changes that render the cargo peptide inactive; the degradation of the foreign peptide; sequestering of the peptide a endosomes or the ability of the CCP sequence to trigger a biological response, such as mast cell degranulation (e.g. positively charged CCP might function as basic secretagogues of mast cells).

Indeed, this appears to be the case for fusion of CCP with either $G\alpha i_3$ or $G\alpha t$. The data from applicants' laboratory and from the Jones *et al.* group demonstrate that not any CCP can maintain the biological activity of $G\alpha i_3$ or $G\alpha t$. Of four CCPs, only KFGF was the only CCP able to both internalize and maintain the inhibitory activity of both $G\alpha i_3$ and $G\alpha t$. Thus the combination provides a surprisingly advantageous result that was not predictable from the prior art.

I do note the Examiner's statement on page 7 that the table on page 9 with reference to the prior literature describing the various CCPs fail to demonstrate that Lin's CCP is unpredictable as a delivery tool. While this is true, there was no academic reason *a priori* to believe that any of the other CCPs would fail to deliver $G\alpha i_3$ and $G\alpha t$ while maintaining its expected biologically activity. But the evidence established by the record indicates that this is not true. There is obviously something special about the two mast cell activation inhibitors or with Lin's CCP that makes the claimed combination functional compared to the other three CCPs.

For these reasons, I conclude without hesitation that the claimed combinations of AAVALLPAVLLALLAP with either $G\alpha i_3$ or $G\alpha t$ to yield a functional inhibitory effect on mast cell activation in light of failure with three other CCPs of equal status was unpredictable, surprising and of great value.

This Declarant has nothing further to say.

Dated: May 6 2007

Dr. Ehud Razin Ehud Razin

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CURRICULUM VITAE

Name:	Ehud Razin
Birthdate:	July 14, 1947
Marital Status:	Married (Michal), two children: Ayelet (1979), Jonatan (1986).
Title:	Professor of Biochemistry, Hebrew-University, Hadassah Medical School.
	Dr. Marcus Rabwin Chair in Cancer Research
Research Interests:	Biology of Mast Cells

EDUCATION:

1965 - 1968	Captain, Israeli Army
1970 - 1973	B. Sc. Biology - Hebrew University of Jerusalem
1973 - 1975	M. Sc. Microbiology - Hebrew University of Jerusalem
1976 - 1980	Ph.D. Immunology - Weizmann Institute of Science

PROFESSIONAL EXPERIENCE:

2005-	Dean Faculty of Medicine Hebrew University
2001-2005	Chairman of the Faculty's Planning & Development Committee
1998-2001	Chairman Biochemistry Department
1996-	Professor of Biochemistry
1997-8	Visiting Scientist of NIAMS, NIH
1993 July-December	Visiting Scientist, NIH, U.S.A.
1991-1996	Assoc. Professor in Biochemistry, Hebrew University of Jerusalem
1987 - 1991	Senior Lecturer in Biochemistry, Hebrew University of Jerusalem.
1983 - 1987	Lecturer in Biochemistry, Hebrew University of Jerusalem.
1982 - 1984	Research Fellow - Immunopharmacology, Harvard Medical School, Boston, MA, USA.
1980 - 1981	Research Fellow - Immunology, Memorial Sloan-Kettering Cancer Centre, NY, USA.
1989 - 1990	Visiting Professor, Biomedical Research Centre, UBC, Vancouver, Canada.
1987 - 1989	Consultant, Syntex Research Co., Palo Alto, CA, USA

AWARDS:

1979	DAAD Scholarship
1980	Chaim Weizmann Fellowship

SOCIETIES:

1983	American Association of Immunologists

1994 CoLLEGIUM INTERNATIoNALE ALLERGoLoGICUM (CIA).

1998 American Society for Biochemistry and Molecular Biology.

Ehud Razin:

Publications

1. Razin, E., Bauminger, S., Globerson, A. Effect of prostaglandins on phagocytosis of sheep erythrocytes by mouse peritoneal macrophages. J Reticuloendothel Soc 1978; 23: 237-42.
2. Razin, E., Zor, U., Globerson, A. Function of macrophage prostaglandins in the process of phagocytosis. Adv Exp Med Biol 1979; 121: 413-7.
3. Razin, E., Globerson, A. The effect of various prostaglandins on plasma membrane receptors and function of mouse macrophages. Adv Exp Med Biol 1979; 114: 415-9.
4. Razin, E., Razin, M., Lohmann-Matthes, M.L. The role of prostaglandins in the development of macrophages from bone marrow cells. J Reticuloendothel Soc 1980; 27: 377-82.
5. Razin, E., Rivnay, B., Globerson, A. Prostaglandins as modulators of macrophage development from bone marrow. J Reticuloendothel Soc 1981; 30: 239-46.
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* Faculty of 1000
** Faculty of 1000 top 10 percent.

11. RELATED PROCEEDINGS APPENDIX

None